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Synthesis of a terbenzimidazole topoisomerase I poison via iterative borinate ester couplings

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Abstract—A concise, efficient synthesis is described for a terbenzimidazole that acts as a potent topoisomerase I poison. The strategy involves iterative palladium-catalyzed borinate ester cross-couplings and should be applicable to the synthesis of analogs containing heterocycles other than benzimidazole.

DNA minor groove-binding ligands Hoechst 33258 (**1**) and related terbenzimidazoles such as **2** (Fig. 1) have been shown to be potent poisons of human topoisomerase I (Topo I).[1,2] These also possess high levels of activity against human tumor cell lines in culture, and thus represent promising lead compounds for the development of new anticancer agents. Our interest is in constructing libraries of analogs of **2** containing 5,6-fused aromatic heterocycles other than benzimidazole, with the objective of identifying more effective Topo I inhibitors. Increased activity could result from altered DNA sequence selectivity; while compounds such as **1** and **2** bind selectively at runs of AT base pairs, this preference can be altered by changing the hydrogen bonding capabilities of individual heterocycles.[3–5] Increased activity could also result from more favorable ligand–protein interactions within a Topo I-DNA-ligand complex.

Syntheses of compounds such as **1** and **2** have typically involved construction of the imidazole portion of benzimidazole units by condensation of aryl *ortho*-diamines with carboxylic acid derivatives.[6] This approach is problematic with regard to libraries containing a variety of heterocycles in that an inordinately large number of synthetic precursors would be required. As illustrated in Scheme 1, 1,2,4-trisubstituted benzene derivatives (represented by **3**) would serve as precursors. While the functional group Z in **3** would be determined by the desired identity of the first heterocycle in **4**,

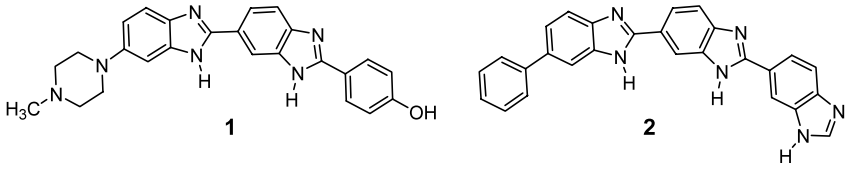
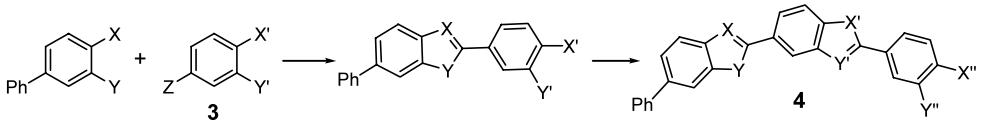


Figure 1. Hoechst 33258 and a phenylterbenzimidazole.



Scheme 1. Generalized synthetic scheme for preparation of analogs of **2** in which formation of the five-membered ring constitutes the homologation step.

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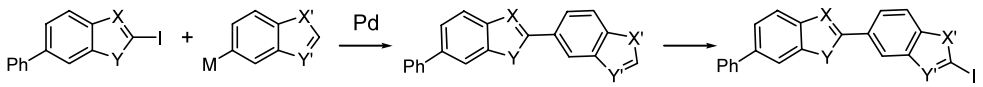
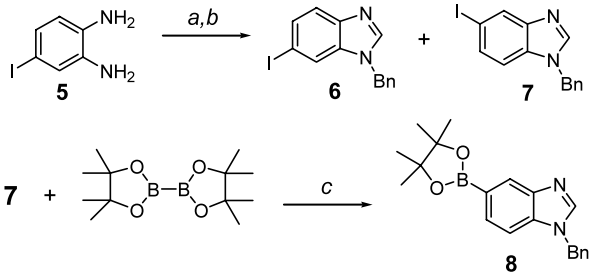


Scheme 2. Generalized synthetic scheme for preparation of analogs of **2** in which palladium-catalyzed addition of an *in-tact* heterocycle constitutes the homologation step.



Scheme 3. *Reagents and conditions*: (a) $HC(OEt)_3$, KSF clay, toluene, reflux, 85%; (b) BnBr, KOH, acetone, 0°C→rt, 90%; (c) $PdCl_2(dppf)$, K_2CO_3, DMF, 75°C, 85%.

functional groups X′ and Y′ would be determined by the desired identity of the second heterocycle in **4**. As a result, a library of 27 of analogs of **2** containing three different heterocycles could require as many as nine precursors (and potentially more depending on the necessary protecting group scheme).[7]

We now report an alternate approach which involves building the oligomer by sequential addition of *in-tact* heterocycles in palladium-catalyzed cross-coupling reactions (Scheme 2). This methodology requires only one precursor (a metalated heterocycle) per heterocycle in the final library, and takes advantage of the fact that iodine can be regiospecifically introduced at the desired position prior to each subsequent coupling.[8,9]

To validate this strategy, we now report the synthesis of **2** by iterative palladium-catalyzed borinate ester couplings. Our synthetic approach required key intermediate **8** (Scheme 3). **5**, prepared from 2-nitroaniline[10,11], was condensed with triethyl orthoformate[12] and benzyl protected to provide a mixture of **6** and **7** in a 55:45 ratio. These were separated by flash chromatography and **7** was then reacted with bis(pinacolato)diboron in the presence of $PdCl_2(dppf)$ to afford **8**.[13]

Coupling of **6** with phenylboronic acid[14] followed by deprotonation with LDA and quenching with diiodoethane[15] provided **9** (Scheme 4). Addition of the second benzimidazole unit was accomplished by reaction of **9** with **8** in the presence of $Pd(PPh_3)_4$;[16] subsequent iodination gave **10**. Coupling of **10** with **8** and deprotection[17] then yielded target compound **2**.

In conclusion, a concise iterative approach for the synthesis of oligomeric heterocycles has been demonstrated. Efforts are currently underway to apply this methodology in the preparation of analogs of **2** containing other heterocycles such as benzoxazole and indole.

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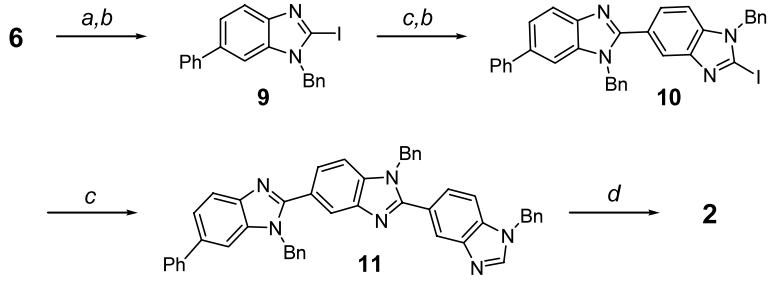

Scheme 4. *Reagents and conditions*: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, aq. 2 M Na_2CO_3/toluene (1:10), 75°C, 91%; (b) LDA, THF, −78°C; ICH_2CH_2I, −78°C→rt, 81%, 83%, respectively; (c) **8**, $Pd(PPh_3)_4$, K_3PO_4, DMF, 50°C, 75, 79%, respectively; (d) 60 PSI H_2, 10% Pd/C, Pd black, hexanes/DMF (1:5), 90°C, 75%.

hydrogen bond donor for the O-2 of thymine and/or the N-3 of adenine on the floor of the minor groove (Pjura, P. E.; Grzeskowiak, K.; Dickerson, R. E. *J. Mol. Biol.* **1987**, *197*, 257–271). Replacing such a donor heterocycle with one that can act as a hydrogen bond acceptor for the amino group of guanine has been a common strategy for altering the sequence selectivity of DNA minor groove binding ligands (Kissinger, K.; Krowicki, K.; Dabrowiak, J. C.; Lown, J. W. *Biochemistry* **1987**, *26*, 5590–5595).

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